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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/884,877	06/20/2001	Henricus Petrus Joseph Te Riele	065691-0230	3654

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EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/884,877	TE RIELE ET AL.	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24,27,28 and 33-49* is/are pending in the application.

4a) Of the above claim(s) *34-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24, 27, 28, 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application filed June 20, 2001 is a continuation in part of 09/147,712, filed February 23, 1999, now abandoned, which is a national stage filing of PCT/EP95/02980, filed July 26, 1995.

Applicants' amendment filed January 12, 2004, has been received and entered. Claims 24 and 33 have been amended. Claims 25, 26, 29-32 have been canceled. Claims 24, 27, 28, 33-49 are pending.

Election/Restriction

Applicant's election with traverse of Group I, in Paper No. 13 was acknowledged. No new arguments are provided in Applicants' instant amendment, Therefore, the requirement is maintained for the reasons of record and still deemed proper.

This application contains claims drawn to an invention nonelected with traverse in Paper No. 13. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claims 24, 27, 28, 33-49 are pending. Claims 34-49 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 13. Claims 24, 27, 28 and 33 are currently under examination.

Oath/Declaration

The substitute declaration mailed October 7, 2003 is in compliance with 37 CFR 1.67(a) with respect to the non-initialed alterations, however, as indicated in the previous office action, the application was filed with an unexecuted declaration and a preliminary amendment to the specification. The substitute declaration does not indicate that a preliminary amendment was submitted in the filing of the instant application (see first page of declaration). Thus it fails to state that the person making the oath or declaration has reviewed and understands the contents of the specification, including the claims, as amended by any amendment specifically referred to in the oath or declaration.

Specification

The disclosure objected to because the same priority was recited twice in the first line of the specification is withdrawn.

Examiner has reviewed the prosecution of the application and acknowledges, as Applicants note, that the specification filed December 26, 2001 is a substitute specification containing the amendment to the first line of the specification. The preliminary amendment was errantly inserted into the substitute copy of the specification instead of the original specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 33 stands rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants note the basis of the rejection and indicate that applicants are in the process of depositing dMsh2-9 the cell line. Applicants request that the rejection be held in abeyance until Applicants have provided the required affidavit or statement. See Applicants amendment page 7, Section III.

Applicants request is noted, however a rejection can not be held in abeyance. Applicants do not provide any other arguments in traverse of the rejection, therefore the rejection is maintained for the reasons of record.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 27 and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, claim 27 depends on cancelled claim 26 and therefore it can not be determined what embodiments both claims 27 and 28 would encompass.

It is noted that claim 26 was dependent on claim 24 and that now the limitations of claim 26 have been incorporated into claim 24. For the sake of compact prosecution, claim 27 will be interpreted for the purposes of other rejections to be dependent on independent claim 24.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 24 and 27 rejected under 35 U.S.C. 102(b) as being anticipated by Reenan *et al.* (Genetics 132:975-985) is withdrawn.

Applicants indicate that that the claims have been amended and the teaching of Reenan *et al.* no longer anticipate the claimed invention. See Applicants amendment page 7, start of Section IV.

Amendments to the claims to encompass "a mammalian cell" has differentiated the claimed invention from the yeast cells disclosed by Reenan *et al.*

Claims 29, 30 and 32 rejected under 35 U.S.C. 102(b) as being anticipated by Umar *et al.* (JBC 269:14367-14370) is withdrawn.

Claims 29, 30 and 32 rejected under 35 U.S.C. 102(a) as being anticipated by Orth *et al.* (PNAS 91:9495-9499) is withdrawn.

Cancellation of the claims has rendered the basis of the rejection moot. See Applicants amendment pages 7-8, Section IV.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 24, 27, 28 and 32 rejected under 35 U.S.C. 103(a) as being unpatentable over Varlet *et al.*, Genbank accession number X81143, and Berns *et al.* (US Patent 5,789,215 or WO 93/04169) is withdrawn.

Applicants summarize the basis of the rejection (first paragraph) and the requirements of establishing a *prima facie* case (beginning of second paragraph). Applicants argue that none of the references teach that both copies the Msh2 gene need to be deleted as required by the instant

claims. See Applicants amendment, pages 8-9, Section V. Applicants arguments have been fully considered, and found persuasive.

Specifically, the references fail to provide all the limitations set forth in the claims in particular providing a disruption in both alleles of the Msh2 gene. Varlet provides evidence to support the art accepted role of Msh2 in DNA repair and provides detailed evidence to support its role in mismatch repair (see summary in abstract for role of Msh2 and title indicating activity of the gene product), however the details of the experiments are insufficient to conclude that disruption of both copies would be required for an observable phenotype. Berns provides the necessary methodology for practicing the instantly claimed method, and provides general motivation and the specific guidance to disrupt both copies of a gene in a cell, however because a phenotype could arise from the disruption of one copy, the general motivation to disrupt both copies would be considered insufficient.

Claims 24, 27, 28 and 32 rejected under 35 U.S.C. 103(a) as being unpatentable over Varlet *et al.*, Genbank accession number X81143, and Berns *et al.* (US Patent 5,789,215 or WO 93/04169) in view of Orth et al. (PNAS, 1994).

At the time of the claimed invention Varlet *et al.* teaches that homologs of Msh2 were known for several species including the mammals mouse and human (summary in figure 1). Further, Varlet *et al.* summarize the prior art and teach that Msh2 in lower eukaryote was associated with mismatch repair. In higher eukaryotes, Varlet *et al.* summarizes that mutations and absence of the Msh2 gene in humans is associated with hereditary non-polyposis colorectal cancer (HPNCC), and the predisposition of a patient to tumor formation (pages 5723-4, bridging

paragraph). The predisposition to tumor formation associated with the loss of Msh2 in tumors was consistent with the loss mismatch repair in *in vitro* systems where the biochemistry of Msh2 was previously analyzed and described in the prior art (page 5723, first paragraph). To analyze homologs of Msh2 previously described in the art, Varlet *et al.* describe the isolation of the mouse Msh2 coding sequence (bridging pages 5724-5725) and indicate that the mouse sequence was deposited as X81143 (see Genbank listing). In characterizing the endogenous expression of Msh2 in the mouse Varlet *et al.* demonstrate a ubiquitous mRNA expression pattern throughout most of the tissues tested (figure 3). Varlet *et al.* note that the expression pattern in the mouse is consistent with replication, however in view of the limited spectrum of tumors in patients with hereditary non-polyposis colorectal cancer the tissue specific role of Msh2 'in HNPCC patients is surprising' (page 5727, top of first column). Varlet *et al.* propose several possible explanations for the observed results and indicate 'further study of the biochemistry (in Xenopus egg lysates) and of the genetics (in mouse) of mismatch repair will shed new light on its [Msh2] role in the maintenance of the integrity of eukaryotic genome, and in the development of cancer (page 5727, final paragraph). Orth *et al.* teaches that in mammals, in particular humans, the characteristic of genetic instability in cell requires that both copies of MSH2 be disrupted. More specifically, Orth *et al.* teach that an individual can be heterozygous for a mutation of MSH2, however it is only as a consequence of the loss of both copies that a results in a phenotype characterized by genetic instability as seen in the resulting tumors as observed in ovarian cancer.

Varlet *et al.* indicate that further research is required to address their hypothesis explaining the limited spectrum of tumor formation *in vivo* in patients with mutant Msh2 alleles, and provide the suggestion to use the mouse model however Varlet *et al.* do not provide the

specific guidance to provide such a model system. At the time of filing transgenic mice were used to provide *in vivo* models of human diseases. Both references by Berns *et al.* teach a method of generating transgenic animals wherein a gene of interest is disrupted. Specifically, Berns *et al.* teach that a gene of interest in the genome of a mouse can be disrupted by generating a targeting construct wherein a homologous sequence to the gene of interest is modified by the insertion of a selectable marker such as hygromycin ('215 column 5, lines 26 and exemplified in figures and working examples), and using said targeting construct to achieve disruption of the gene of interest in a mouse embryonic stem cell through homologous recombination methodology in the mouse embryonic stem cell ('215 summarized in abstract). Berns *et al.* teach that modifications to the genome can be an insertion, deletion, or substitution within the gene of interest wherein the site specific integration of the targeting construct results in a modification which disrupts expression of the gene product ('215 column 4, lines 59-67). Finally, Berns *et al.* teach that upon generating a mouse embryonic stem cell with the desired alteration in its genome, the embryonic stem cell can be used to generate knock-out transgenic animals wherein one or both copies of the genes of interest contain the modification ('215 paragraph bridging columns 15 and 16).

Varlet *et al.* teach that further *in vivo* analysis of the role of Msh2 is required and that the study of the genetics in mice will provide further insight on the development of cancer, therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to generate animal model system wherein the specific Msh2 sequences disclosed by Varlet *et al.* are disrupted in the cells of mouse. Berns *et al.* provide the methodology to generate gene disruptions in embryonic stem cells through homologous

recombination and provide guidance to for the generation of a transgenic mouse from said genetically modified embryonic stem cell. One having ordinary skill in the art would have been motivated to use the methods described by Berns *et al.* to disrupt the expression of the Msh2 gene because Varlet *et al.* teach that it is the absence of expression of the Msh2 gene that was associated with the mutant phenotype in cells and in tumors isolated from patients. Further, by providing a mouse embryonic stem cell with the endogenous Msh2 gene expression disrupted using the methods of Berns *et al.*, a knock-out animal can be produced to test the hypothesis set forth by Varlet *et al.* There would have been a reasonable expectation of success to generate a mouse embryonic stem cell with a disrupted Msh2 gene using the methods of Berns *et al.* given the successful results demonstrated by Berns *et al.* for the Rb gene in the working examples and his teaching that other knock-out animals have been made using similar methodology.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Claims 29, 30 and 31 rejected under 35 U.S.C. 103(a) as being unpatentable over Varlet *et al.*, Genbank accession number X81143, and Berns *et al.* (US Patent 5,789,215 or WO 93/04169) in view of Promega Protocols and Applications Guide is withdrawn.

Cancellation of claims 29-31 has rendered the basis of the rejection moot.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (571) 272-0739.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (571) 272-0734.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (571) 272-0532.

Joseph T. Woitach

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